

REMARKS

This Amendment is being submitted in response to the Final Official Action dated 29 July 2009. Claims 26, 27, 28, 30, 32 and 36 are amended, claims 33-35 are herein canceled, and new claim 41 is added. Thus, claims 26-28, 30, 32 and 36-41 are pending in this application.

Claims 26-28, 30, 32, and 36-40 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite because the active method step is not sufficiently linked to the preamble of the claim. Claims 26 and 36 are herein amended as suggested to link the active method step to the antecedent preamble, e.g., "administering to said patient in need thereof".

Claims 26-28, 30, 32, and 36-40 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite because metes and bounds of the limitation, " ... further comprising a calibrated administration frequency ... " so as to continuously maintain a decreased $[GSH]^2/[GSSH]$ ratio in malignant cells within a range of from 15 to 75 hours in order to span at least one cell cycle, are not clear. The Examiner maintains that it is not apparent what "administration frequency" is encompassed by the instant claims. The Examiner posits that an active agent with a long in vivo half-life might only need to be administered once to achieve the claimed result, whereas an active agent with a short in vivo half-life might have to be repeatedly administered to achieve the claimed maintenance of decreased $[GSH]^2/[GSSH]$ ratio in malignant cells within a range of from 15 to 75 hours in order to span at least one cell cycle. The Examiner's logic is correct but tends to support the claim limitation rather than its indefiniteness. The specification provides ample guidance as to dosage, at [0080] the $[GSH]^2/[GSSG]$ -decreasing agent(s) are preferably administered cumulatively in an amount of from about 0.01 g to about 1-8

grams per day. At [0077] the “administration frequency” maintains continuously the E of the cancer cell at about -190 to -200 mV for ...1-3 the cell cycle periods and within the range of from about 15 to about 72 hours, preferably from about 20 to about 60, more preferably from about 25 to about 50, still more preferably from about 30 to about 45 hours. The specification also makes it clear that the exact administration frequency will depend on the type of tissue and the type and stage of the tumor, and “while some experimentation may be required to determine optimum dosages in order to achieve a particular biological response, such experimentation is not considered to be undue” and reciting “an effective amount” in terms of the function which is to be achieved without reciting a specific amount of active ingredient present does not render a claim indefinite.

Ex Parte Werner Skuballa, Helmut Dahl, Bernd Raduchel, Helmut Vorbruggen And Olaf Loge, Appeal No. 86-1591, June 2, 1989. Nevertheless, in case the Examiner’s rejection is more semantic than substantive, Applicant herein amends claims 26 and 36 to eliminate “calibrated administration” and instead define a “*pharmaceutically effective dosage of said drug further comprising a plurality of separate dosage units of said drug administered in a cumulative amount of from 0.01-8 grams per day of said E-increasing agent as needed to continuously maintain said decreased [GSH]2/[GSSG] ratio in the malignant cells and consequently continuously maintain said dephosphorylated state of the RB in said cancer cells within a range of from 15 to 75 hours in order to span at least one cell cycle, and a minimum effective amount of said enzyme deactivating agent to cause regression of said tumor.*” As per MPEP 2173.02 the requirement for definiteness of 35 U.S.C. 112, second paragraph, is whether the claim cites a reasonable degree of particularity and distinctness, not whether more suitable language or modes of expression

are available. Some latitude in the manner of expression and the aptness of terms should be permitted even though the claim language is not as precise as the examiner might desire. If in light of the amendments the Examiner still harbors concern he is invited to suggest claim language to improve the clarity or precision of the language used.

Claims 26-28, 30, 32, and 38-40 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite due to the recited abbreviations BCNU and BSO. Applicant herein amends claims 26 and 36 so that the first recitation of these abbreviations is preceded by the full meaning of the abbreviated terms.

Claims 36-39 were rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. According to the Examiner, the claims recite a genus of compounds that is defined only by biological activity (i.e., "E-increasing agent" and "enzyme deactivating agent"), and there is insufficient written description of the claimed agents. The specification only discloses GSH oxidizing agents that must not only have the activity claimed, but must also treat tumors and be capable of maintaining a decreased $[GSH]^2/[GSSH]$ ratio in malignant cells. The examiner contends that Applicants have not demonstrated possession of the claimed "E-increasing agent" and "enzyme deactivating agent" and which further are antitumor agents and have provided no direction as to (a) what subset of compounds out of all possible compounds that exist in the art would have been reasonably expected to have said activity. Applicant herein amends claim 36 to specify said that the two E-increasing agents are disulfiram and curcumin, and the two enzyme deactivating agents are bis-chloronitrosourea (BCNU) and buthionine sulfoximine (BSO), and there is ample written description of these claimed agents.

Claims 26 and 32 were rejected under 35 U.S.C. 103(a) as being unpatentable over Cen et al. (Molecular Cancer Therapeutics, January 2002, vol. 1, pages 197-204) in view of Bailey et al. (Journal of the National Cancer Institute, 1997, vol. 89, pages 1789-1796).

Bailey '97 teaches only that continuous administration of BSO for 48-72 hours inhibits glutathione biosynthesis (lowers the GSH concentration) and increases cytotoxicity of melphalan given *subsequent* to the BSO regimen. The explicit relationship of $[GSH]^2/[GSSG]$ to E, and the requirement that E has to be raised high enough to dephosphorylate RB, is not disclosed, nor is Applicant's claimed co-administration of one or two specific E-increasing agents disulfiram and curcumin plus one/two enzyme deactivating agents bis-chloronitrosourea (BCNU) and buthionine sulfoximine (BSO), nor is Applicant's claimed dosage in *separate dosage units of said drug administered in a cumulative amount of from 0.01-8 grams per day of said E-increasing agent as needed to continuously maintain said decreased $[GSH]^2/[GSSG]$ ratio in the malignant cells and consequently continuously maintain said dephosphorylated state of the RB in said cancer cells within a range of from 15 to 75 hours in order to span at least one cell cycle, and a minimum effective amount of said enzyme deactivating agent to cause regression of said tumor.*

Cen et al. provides an in vitro comparative analysis of apoptosis and cellular glutathione content between DSF and BSO treatment. Though they tried a combination of DSF and BSO, they found a "lack of significant DSF/BSO effect (as compared with DSF alone)" and attributed this to maximal depletion of GSH by BSO, and so no added effect of DSF. As stated on the attached Declaration Under Rule 1.132, the BSO

remains in continuous contact with the cancer cells for the duration of the treatment so that the dephosphorylated state of RB is continuously maintained. Consequently, the in vitro effectiveness of BSO by itself is at the maximum and there is no motivation to add or combine other agents. Cen et al. does not contemplate the fact that in vivo agents do not inherently remain in continuous contact with the cancer cells for the duration of the treatment due to the action of GR and/or the gamma-GCS enzymes, and does not contemplate (indeed teaches away from) adding other agents that deactivate the GR and/or the gamma-GCS enzymes. Clearly, the combination of the four agents claimed in claims 26 and 36 provide in vivo synergy when administered at the recited dosage. Contrary to the Examiner's statement, Cen et al. does not suggest co-administration of BSO and DSF (let alone Applicant's four agents) but instead teaches away from it.

Nevertheless, the Examiner contends that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have administered disulfiram and BSO *to deplete intracellular glutathione (BSO) and reduce the $[GSH]_2/[GSSG]$ ratio (disulfiram) as recited in the instant claims*. This is not correct. Cen et al. expressly notes that intracellular glutathione was remarkably depleted with BSO treatment, but that the "cellular GSSG level in BSO-treated melanoma cells was too low to be measured because of a significant depletion of total glutathione." If the $[GSH]_2/[GSSG]$ ratio could not be measured in vitro with the BSO/DSF combination, then it could not possibly have been obvious to administer disulfiram and BSO in vivo to deplete intracellular glutathione (BSO) and reduce the $[GSH]_2/[GSSG]$ ratio (disulfiram) as recited in the instant claims.

Moreover, Applicant's claimed invention is more than just co-administration of

disulfiram and BSO for 3-4 days. Rather, it is co-administration of two E-increasing agents disulfiram and curcumin plus two enzyme deactivating agents bis-chloronitrosourea (BCNU) and buthionine sulfoximine (BSO) in periodic dosage units in a cumulative amount of from about 0.01 g to about 1-8 grams per day, as needed to continuously maintain said decreased $[GSH]^2/[GSSG]$ ratio in the malignant cells and consequently continuously maintain said dephosphorylated state of the RB in said cancer cells within a range of from 15 to 75 hours in order to span at least one cell cycle. DSF and BSO as suggested by the schedules taught in Cen et al. or Bailey et al. would not have the effect of continuously maintaining decreased $[GSH]^2/[GSSG]$ ratio in the malignant cells and consequently continuously maintaining the dephosphorylated state of the RB in melanoma cells within a range of from 15 to 75 hours in order to span at least one cell cycle, simply because it did not have that effect. It is not Applicant's burden to submit evidence that co-administration of disulfiram and BSO for 3-4 days as taught in Cen et al. or BSO administered by the schedules taught in Bailey et al. would not have the Applicant's recited result. This presumes that the recited result would be inherent and belies the Examiner's mindset that Applicant has discovered a previously unappreciated property of a prior art composition.¹ Applicant has discovered that co-administration of disulfiram, curcumin, BCNU and BSO in a periodic dosage as specifically claimed per day continuously maintains the dephosphorylated state of RB for

¹ The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); In re Oelrich, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.

15 to 75 hours in order to pharmaceutically induce apoptosis in vitro. This is synergy which is not present in vivo, and it is Applicant's burden to submit evidence of that synergy. The synergy is stated in detail in the present specification and is supported at length in Applicant's 132 declarations, and it would not have been obvious to combine Cen et al. with Bailey et al. to achieve Applicant's recited result.

Claims 26, 30, and 32 were rejected under 35 U.S.C. 103(a) as being unpatentable over Ali-Osman et al. (Mol. Pharm., 1996, vol. 49, pages 1012-1020) and Marikovsky (USP No. 6,288,110; Issued Sep. 11, 2001) in view of Bailey et al. (Journal of the National Cancer Institute, 1997, vol. 89, pages 1789-1796).

Ali-Osman merely suggests that BCNU mitigates the cytotoxicity of BSO. This suggests the combination of BSO and BCNU. Marikovsky teaches that administering DSF once per day will inhibit angiogenesis (growth of new capillary blood vessels), with the intention of treating angiogenesis-dependent disorders. The Examiner fails to explain how this translates to tumor cell apoptosis, but apparently analogizes it to disulfiram induced apoptosis of capillary endothelial cells (Figure 4). Capillary endothelial cells are not tumor cells. As above, Bailey '97 teaches only that continuous administration of BSO for 48-72 hours inhibits glutathione biosynthesis (lowers the GSH concentration) and increases cytotoxicity of melphalan given subsequent to the BSO regimen. From this the Examiner reasons that it would have been prima facie obvious to one of ordinary skill to have administered BSO and BCNU in combination with disulfiram to a subject having cancer.

Pre-administration of BSO/BCNU, BSO to increase cytotoxicity of melphalan and BCNU to mitigate the cytotoxicity of BSO, followed by disulfiram induced apoptosis of

capillary endothelial cells simply does not add up to Applicant's claimed co-administration of disulfiram, curcumin, BCNU and BSO in a periodic dosage of 0.01 g to about 1-8 grams per day continuously maintains the dephosphorylated state of RB for 15 to 75 hours in order to pharmaceutically induce apoptosis in vitro. This is especially true in light of the synergistic in vivo effect established by Applicant. Applicant has now presented two working examples as factual evidence demonstrating that an effect not expected from the teachings of the prior art is observed when tumors are treated with disulfiram, curcumin, BCNU, BSO in accordance with Applicant's specifications, and there is no such suggested motivation to pursue this combination in the cited prior art. Amended claims 26, 30, and 32 are patentably distinguished.

Claims 26, 30, and 32 were also rejected under 35 U.S.C. § 103(a) as being unpatentable over US Patent No. 6,589,987 to Kennedy in view of Nagendra et al. (Alcohol, 1994, vol. 11, pages 7-10), Huang et al. (The FASEB Journal, 2001, vol. 15, pages 19-21; published online 11/9/2000), Ali-Osman et al. (Mol. Pharm., 1996, vol. 49, pages 1012-1020), and Hoffman et al. (1. Theor. Biol., 2001, vol. 211, pages 403-407). The Examiner reads Kennedy for the proposition that Disulfiram can be administered in combination with another anticancer agent (col. 3, lines 10-13 and col. 7, lines 8-18). Kennedy suggests that thiuram disulfide and a heavy metal ion can be administered in combination with another anticancer agent, but never suggests what the other agent might be. Nagendra suggest that disulfiram decreases GSH2/ GSSH but is silent with respect to treating tumors. Huang et al. suggests that a decrease is GSH achieved with BSO may

result in a decrease in cell growth. Ali-Osman suggests that BCNU mitigates the cytotoxicity of BSO. Hoffman et al. is cited to tie these disparate teachings together, e.g for the proposition that an elevated redox potential can inhibit phosphorylation of RB protein, which in turn will stop cell proliferation, suggesting the treatment of cancers having an operative retinoblastoma (RB) protein via changes in redox potential (and also that agents that decrease GSH will increase redox potential). However, as Fig. 1 of Hoffman illustrates, selectivity requires that the E of the normal cells be below the threshold to prevent their death. This limits the treatment to administering the agents directly into the tumor tissue of the subject being treated to avoid any contact of the normal cells with the E- increasing/ maintaining agents. Such excludes systemic administration of these agents at all, let alone *“co-administration of two E-increasing agents disulfiram and curcumin plus two enzyme deactivating agents bis-chloronitrosourea (BCNU) and buthionine sulfoximine (BSO) in periodic dosage units in a cumulative amount of from about 0.01 g to about 1-8 grams per day, as needed to continuously maintain said decreased [GSH]²/[GSSG] ratio in the malignant cells and consequently continuously maintain said dephosphorylated state of the RB in said cancer cells within a range of from 15 to 75 hours in order to span at least one cell cycle.”*

Even if the Examiner is justified in his piecemeal combination, Hoffman et al (2001) teaches incorrectly that the E of normal cells must be below the threshold to obtain selectivity, thereby excluding systemic administration. The mechanism through which Applicants achieve their result is pertinent to the present rejection because the mechanism accounts for the action of GR and/or the gamma-GCS enzymes in vivo (which the prior art does not), and deactivates the GR and/or the gamma-GCS enzymes. Moreover,

Applicant has presented factual evidence (tests) supporting their proposition that the combination of the four agents claimed in claims 26, 30, and 32 provide in vivo synergy when administered at the recited dosage and achieves a result different from other administration frequencies.

Claims 27-28 and 36-40 were also rejected under 35 U.S.C. 103(a) as being unpatentable over Kennedy, Nagendra et al., Huang et al., Ali-Osman et al., and Hoffman et al. and further in view of Ramachandran et al. (Breast Cancer Research and Treatment, 1999, vol. 54, pages 269-278) and Sharma et al. (Clinical Cancer Research, July 2001, vol. 7, pages 1894-1900). According to the Examiner, Ramachandran et al. adds that administration of curcumin to breast cancer cells induced apoptosis in breast cancer cells compared to a very low percentage of apoptosis in mammary epithelial cells, and Sharma et al. likewise teaches that curcumin has been shown to prevent cancer. This is a piecemeal combination of prior art that ignores the unique type in vivo synergistic effect of Applicant's specific combination of agents and specific regimen. [See attached Declaration of Arnold Hoffman]. Moreover, Sharma et al. did not show that the curcumin actually helped the patients or shrunk the cancer. They noted that the "Mechanisms by which curcumin prevents cancer are thought to involve up-regulation of carcinogen-detoxifying enzymes, such as GSTs." The regimen comprised the administration of curcumin once daily for 4 months. There is no teaching or suggestion of a particular dosage frequency or parameter, and as described above choosing the correct dosage frequency is essential in the redox therapy as recited in claim 26 (as amended). Dosing with curcumin once per day for 4 months in no way anticipates the teaching of the subject patent to maintain E above the threshold for up to 75 hours. Moreover, one

would not be led from Sharma's method of daily dosing to the more frequent dosing that may be required to continuously maintain E above the threshold even if his method had shown any efficacy as a treatment for cancer, which it did not. [See the attached Declaration of Arnold Hoffman]. Therefore, Sharma et al. do not teach or suggest raising the E/dephosphorylate pRB with E-increasing agents and maintaining the raised E/dephosphorylated state of pRB at all, let alone by any synergistic combination of both 1) a E-increasing agent (disulfiram and/or curcumin); plus 2) an enzyme deactivating agent (BCNU and/or BSO). Since claim 26 as amended recites both aforesaid requirements, claim 26 is patentably distinguished over the foregoing combination in further view of Ramachandran et al. and Sharma et al.

Claims 26-27, 30, 32, and 36-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoffman (WO 02/056823; Published July 25, 2002) in view of Ali-Osman et al. (Mol. Pharm., 1996, vol. 49, pages 1012-1020) and Cen et al. (Molecular Cancer Therapeutics, January 2002, vol. 1, pages 197-204). The Examiner credits Hoffman with a method of treating malignancies through control of the redox state or environment of the cell, comprising administering a GSH-decreasing agent (Abstract). However, Hoffman WO 02/056823 incorrectly teaches that the treatment will only be selective if the E of the normal cells is not high enough to dephosphorylate the RB. The subject application discloses that the Redox Therapy is selective even if the E of the both the normal as well as the cancer cells is high enough to dephosphorylate the RB. In short, the present application relies on an intrinsic selectivity that allows for systemic administration. The disclosure of a redox cycle within the normal cell cycle, and its absence in a cancer cell cycle, as described in the subject application (see Scheme 1),

reveals another basis for selectivity. That is, normal cells exit mitosis and enter G1pm and from there enter Go where they can remain indefinitely. According to the subject application the cancer cells skip G1pm, cannot enter Go but proceed directly from mitosis to G1ps. Increasing E above the threshold results in all the cells entering G1pm where they can remain for only a limited time. The normal cells enter Go where they can remain indefinitely. Cancer cells however cannot enter Go. They can only remain in G1pm for a limited time beyond which they will undergo apoptosis. The subject patent discloses that this phenomena can be exploited to serve as a basis for an intrinsic selectivity that kills only the cancer cells but does not harm normal cells. This allows for a systemic administration of the E- increasing and maintaining agents. Systemic administration is noted in the subject claims as amended. These teachings are not obvious to one in the art as they were developed subsequent to the filing the Hoffman WO application. Claims 27 and 36 both require “continuously maintaining a dephosphorylated state of the RB in said cancer cells to induce apoptosis thereof” while Hoffman WO 02/056823 incorrectly teaches away from this. Hoffman WO 02/056823 generically names GSH-depleting agents such as BSO and/or curcumin, and BCNU as well. However, Hoffman does not teach or suggest Applicant’s systematic administration of one (claim 26) or two (claim 36) specific E-increasing agents disulfiram and curcumin plus one/two enzyme deactivating agents bis-chloronitrosourea (BCNU) and buthionine sulfoximine (BSO), nor is Applicant’s claimed dosage in *separate dosage units of said drug administered in a cumulative amount of from 0.01-8 grams per day of said E-increasing agent as needed to continuously maintain said decreased [GSH]2/[GSSG] ratio in the malignant cells and consequently continuously*

maintain said dephosphorylated state of the RB in said cancer cells within a range of from 15 to 75 hours in order to span at least one cell cycle, and a minimum effective amount of said enzyme deactivating agent to cause regression of said tumor. If the administration frequency of any prior art combination of agents that raise the high E/dephosphorylated state of the pRB but fails to maintain it, then for several hours after each administration, the E will drop back toward its initial value/ pRB will become phosphorylated. This will promote cell proliferation, nullifying the effectiveness. Therefore, this claim limitation is essential, and yet it is absent in Applicant's PCT Application. None of the other cited references add anything toward this regard. Cen et al. provides an in vitro comparative analysis of apoptosis and cellular glutathione content between DSF and BSO treatment and actually teaches away from the combination of DSF and BSO due to a "lack of significant DSF/BSO effect (as compared with DSF alone)" and attributed this to maximal depletion of GSH by BSO. Applicant maintains that to establish a prima facie case of obviousness the Examiner must identify some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings, there must be a reasonable expectation of success and the combined prior art reference must teach or suggest all the claim limitations. MPEP 2143. As described above, the applicant asserts that the combined references fail to teach or suggest the claim limitations of claims 3 and 5, and further the Examiner has not identified the source of the prior art or the knowledge generally available to one of ordinary skill. As such, the proposed combination of Hoffman WO and Cen et al. is improper, and hence the obviousness rejection is improper in this instance.

Again, Ali-Osman merely suggests that BCNU mitigates the cytotoxicity of BSO

and at best suggests the combination of BSO and BCNU, but adds nothing in the aforementioned regard and so independent claims 26-27 and 36 and depending claims 30, 32, and 36-40 are patentably distinguished.

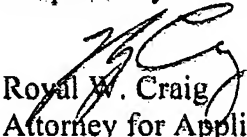
New claim 41 is added to claim a drug *consisting* of disulfram, curcumin, bis-chloronitrosourea (BCNU) and buthionine sulfoximine (BSO), periodically within a range of from 1-8 grams per day as needed to cause an increase in E/decrease in the $[GSH]^2/[GSSG]$ (wherein [GSH] is the concentration of glutathione and [GSSG] is the concentration of glutathione disulfide) ratio in the malignant cancer cells of said tumor and to continuously maintain said decreased $[GSH]^2/[GSSG]$ ratio within a range of from 15 to 75 hours. Consisting is a term of exclusion of any other constituents and further distinguishes the prior art.

Claims 26-27, 30, 32 and 36-40 were provisionally rejected on the ground of non-statutory obviousness-type double patenting over claims 9-15, 20, and 25-28 of copending Application No. 111596,043. The Examiner notes that the conflicting claims are not identical. Indeed, the corresponding claims of the present application were previously canceled and none of the remaining claims require the same agent functionality. The '043 application calls for four agents by function: (i) a compound that oxidizes GSH; (ii) a compound that forms an adduct or a conjugate with GSH; (iii) a compound that inhibits the rate-limiting enzyme of GSH biosynthesis, .gamma.-glutamylcysteine synthetase (GCS); and (iv) a compound that inhibits the enzyme responsible for the conversion of GSSG to GSH, glutathione reductase (GR). The present application calls for four

agents: disulfram, curcumin, BCNU and BSO. The present agents do not correspond one-to-one to the functional elements of the '043 application. Applicant respectfully points out the Examiner may not maintain this as his only remaining rejection, but should instead withdraw it and permit this earlier-filed application to issue as a patent without a terminal disclaimer.

In light of the foregoing amendments and argument, Applicant asserts that all claims are now in condition for allowance. As the amendments do not introduce any new issues into the present application, entry and allowance are believed to be appropriate.

Respectfully submitted,



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